What is Pharmacogenomics?

Personalization of Medications for You!

Michigan State Medical Assistants Conference
May 6, 2006

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MDCH

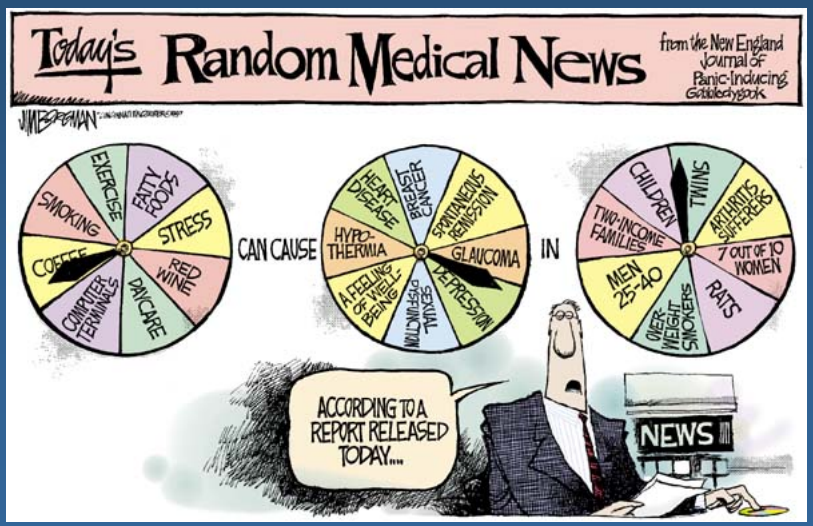
Learning Objectives

- Define genomics and pharmacogenomics
- Understand applications of pharmacogenomics in clinical settings
- Provide an example of pharmacogenomics
- Appreciate possible ethical and legal issues

What determines your risk for disease?

http://www.cdc.gov/genomics/public/file/media/FHpresentation_files/frame.htm

Risk Factors



http://borgman.enquirer.com/weekly/daily_html/1997/04/042797borgman.html

Risk Factors

A risk factor increases your chance of developing a disease or health problem

environment

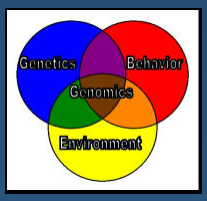
behaviors and lifestyle

*inherited characteristics

*inherited – passed down from parents to children

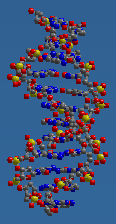
http://www.cdc.gov/genomics/public/file/media/FHpresentation_files/frame.htm

From "Genetics" to "Genomics"



Genetics → ***Genomics***

The science of heredity; refers to a single gene and its effects.



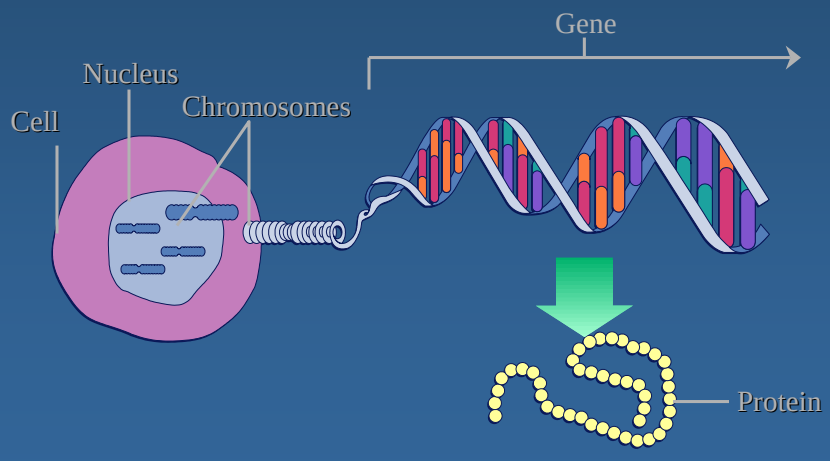
The study of the entire genome including the complex interactions among multiple genes as well as between genes and the environment.

What Does My 'Genome' Mean to Me and My Health?

High School Division Winner

Used with permission of winner of high school division

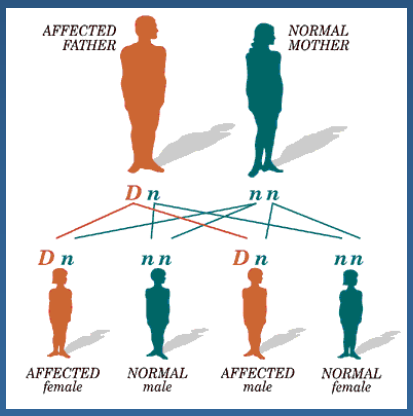
Chromosomes, Genes & DNA



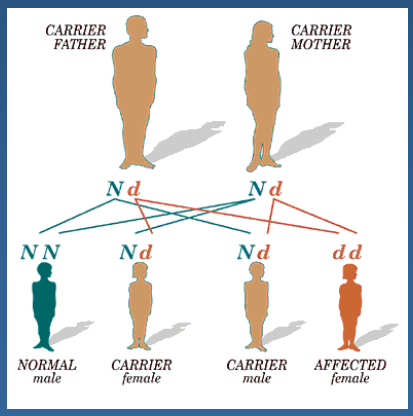
Adapted from *Understanding Gene Testing*, NIH, 1995

Mendelian Inheritance Patterns

Autosomal Dominant



Autosomal Recessive



Genetic Interest Group (GIG): http://www.gig.org.uk

From the simple towards the complex

- Single gene disorders account for a small percentage of the morbidity and mortality experienced by Michigan citizens
- The major causes of morbidity and mortality within the state are common chronic diseases (cardiovascular disease, cancer, stroke and diabetes)
- These common chronic diseases can have complex genetic etiologies

Genetics vs. Genomics

- Genetics focuses on studying genes and how they are passed from one generation to the next (heredity)
- Genomics focuses on understanding how an individual's entire genome interacts with internal and external factors to modify disease susceptibility

Human Genome Project

- Program started in 1991 as a collaboration between NIH and DOE
- Project goals:
  - Identify all genes (20-25,000) in human DNA
  - Determine the sequence of 3 billion base pairs
  - Store information in databases
  - Improve tools for data analysis (bioinformatics)
  - Transfer related technologies to private sector (licensing technologies)
  - Address ELSI issues related to project
- Working draft sequence and analysis published February 2001

http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml

Human Genome Project

http://cagle.msnbc.com/news/gene/gene14.asp

Potential Benefits & Applications

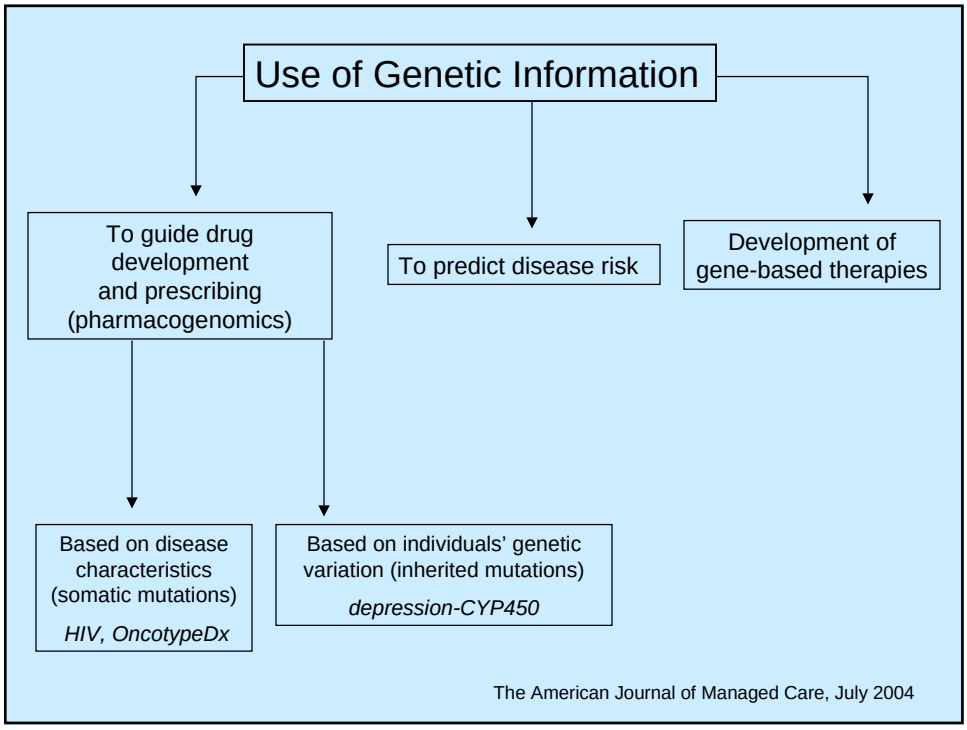
- Molecular medicine
- Energy sources and environmental applications
- Risk assessment
- Anthropology, evolution, human migration
- DNA forensics
- Agriculture and livestock

http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml

Molecular Medicine

- Improve diagnosis of disease
- Earlier detection of genetic predispositions to disease
- Rational drug design
- Gene therapy
- Pharmacogenomics (personalized medicine)

http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml



The American Journal of Managed Care, July 2004

From DNA to Health

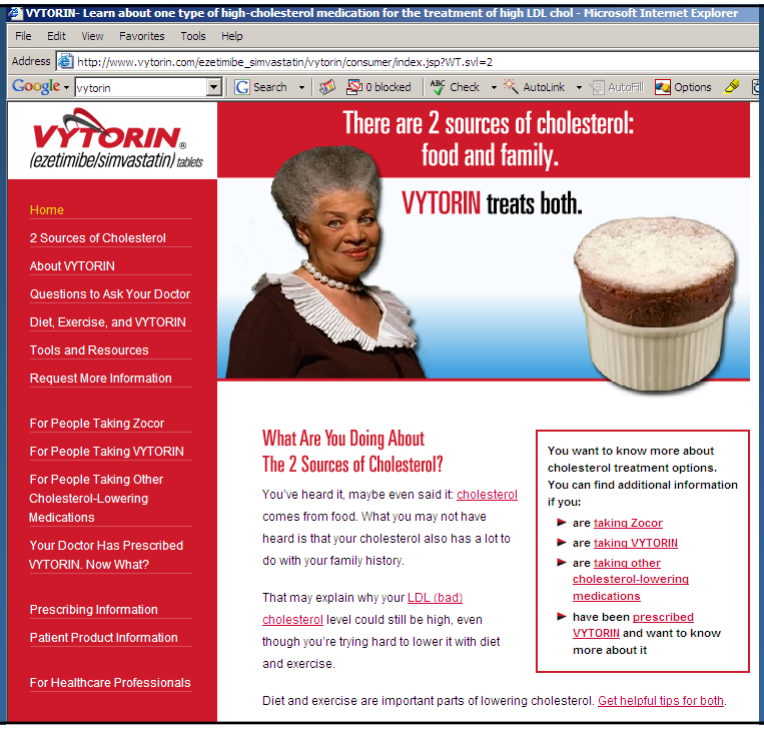
Used with permission of Keith Johnson, PhD- Pfizer

What is Pharmacogenomics?

- Study of how your genetic makeup affects your response to drugs
  (American Medical Association)
- Influence of DNA-sequence variation on drug effects
  (Roche Diagnostics)
- Combines biochemistry and other traditional pharmaceuticals with understanding of common DNA variations

Science or Sizzle?

"I don't think that there's merit to these particular claims to stratify vitamins based on ethnicity."
-- Winston Price, past president, National Medical Association



History

- In 1950's, observations that different responses to drugs ran in families and ethnic groups
- In 1990's, the field of pharmacogenomics began, in large part because of Human Genome Project

NEJM 348;6 February 6, 2003

Traditional Pharmacotherapy Results for Patients include:

1) Desired therapeutic actions
2) Partial therapeutic actions
3) No effect from the drug
4) One of above and adverse drug effects

Variability of Drug Effects

- Genetics accounts for 20-95% of variability in drug disposition and effects
- Non-genetic factors include compliance, age, state of health, diet, smoking, organ function, concomitant therapy, drug interactions, and nature of disease

NEJM 348;6 February 6, 2003

A New Way to Practice Medicine?

- Currently, medications prescribed through "trial and error"
- With pharmacogenomics, individualizing prospective drug therapy to:
  - Maximize effectiveness
  - Minimize side effects

Benefits of Pharmacogenomics

- More Powerful Medicines
- Better, Safer Drugs the First Time
- More Accurate Methods of Determining Appropriate Drug Doses
- Advanced Screening for Disease
- Better Vaccines
- Improvements in the Drug Discovery and Approval Process

http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml
www.ama-assn.org/ama/pub/category/2306.html

…and perhaps most importantly,

- Decrease in the Overall Cost of Health Care
  - Number of adverse drug reactions
  - Number of failed drug trails
  - Time for drug approval
  - Length of time patients are on medication
  - Number of medications to find effective therapy
  - Early detection of disease

www.ama-assn.org/ama/pub/category/2306.html

Adverse Drug Reactions

- Over 106,000 people in the US die yearly from adverse reactions to correctly prescribed doses of drugs
- In top 6 leading causes of death in the US
- $4.3 billion per year cost in excess medical care

http://gslc.genetics.utah.edu/units/pharma/phwhatis/

Clinical Application

Why would one person benefit from an antidepressant, and another suffer severe side effects?

Antipsychotic and Antidepressant Drugs

- Typically “start low and go slow”
- Up to 8 weeks or longer before efficacy known
- Average effective doses based upon “average patients”
- At least 10-25% of SSRI-treated patients are non-responders

Example of Clinical Use

- Cytochrome P450 (CYP)
  - Family of liver enzymes
  - Responsible for metabolizing more than 30 different classes of drugs
  - 55 genes and 25 pseudogenes in humans

http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml

CYP450

- Two genes analyzed by AmpliChip CYP450 Test (first FDA cleared microarray)
  - CYP2D6
    - 19% of marketed drugs
    - Detects 27 allelic variations
  - CYP2C19
    - 8% of marketed drugs
    - Detects 3 allelic variations

http://www.amplichip.us/physicians/abouttheamplichip.php

Single Nucleotide Polymorphisms (SNPs)

- Most Common DNA variations
- Estimated 11 million SNPs in human population with an average of one every 1300 base pairs
- Response to drug often linked to SNPs
- DNA microarrays/chips screen 100,000 SNPs in hours

http://www.roche.com/med_backgr-ampli.htm

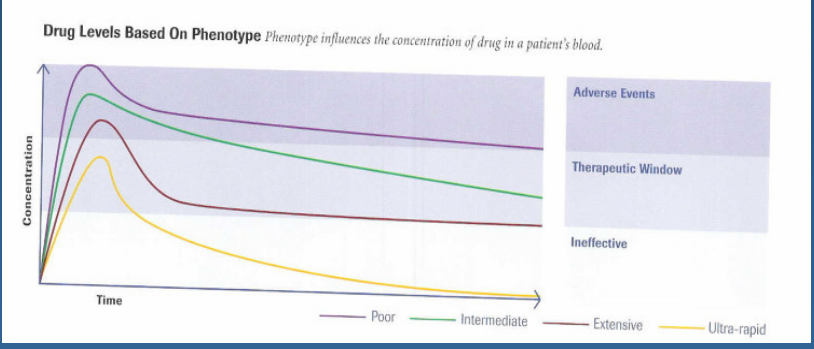
Phenotypes

- Poor Metabolizers (PM)
  - Lack functional enzymes
  - Risks for adverse drug effects (oversedation, postural hypotension, autonomic effects)*
  - For CYP2D6, 7-10% of Caucasians
- Intermediate Metabolizers (IM)
  - Reduced enzyme activity due to deficient allele(s)
  - For CYP2D6, 10-15% of Caucasians
- Extensive Metabolizers (EM)
  - One or two normal alleles
  - For CYP2D6, 73-82% of Caucasians
- Ultrarapid Metabolizers (UM)
  - Multiple gene copies of functional alleles
  - Ineffective at standard doses*
  - For CYP2D6, 1-2% of Caucasians

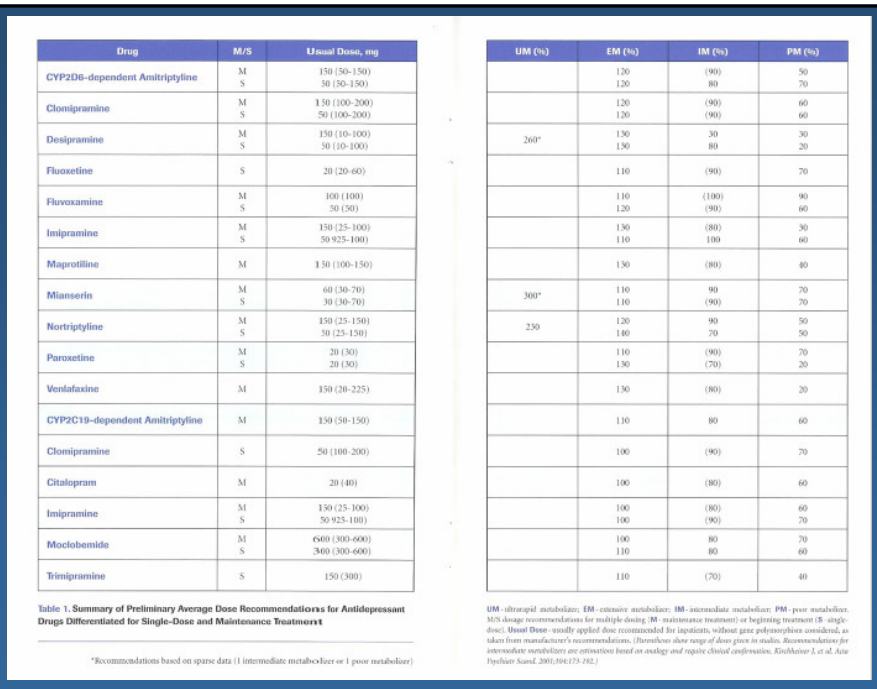
*converse is true for "pro-drugs" (metabolized to active form), such as codeine

http://www.amplichip.us/physicians/abouttheamplichip.php

CYP450



http://www.amplichip.us/physicians/abouttheamplichip.php



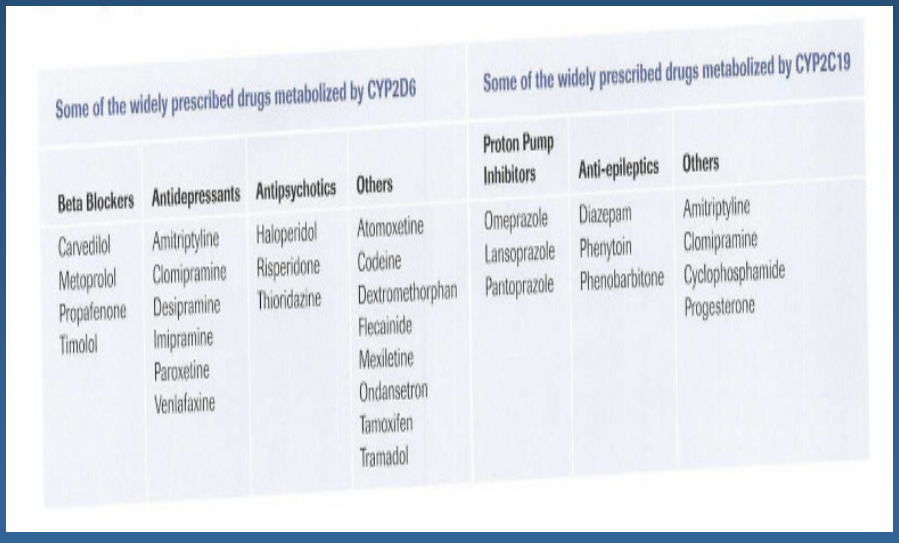
Drug	M/S	Usual Dose, mg	UM (%)	EM (%)	IM (%)	PM (%)
CYP2D6-dependent Amitriptyline	M	150 (50-150)		120	(90)	50
	S	50 (50-150)		120	80	70
Clomipramine	M	150 (100-200)		120	(90)	60
	S	50 (100-200)		120	(90)	60
Desipramine	M	150 (10-100)	260*	130	30	30
	S	50 (10-100)		130	80	20
Fluoxetine	S	20 (20-60)		110	(90)	70
Fluvoxamine	M	100 (100)		110	(100)	90
	S	50 (50)		120	(90)	60
Imipramine	M	150 (25-100)		130	(80)	30
	S	50 925-100)		110	100	60
Maprotiline	M	150 (100-150)		130	(80)	80
Mianserin	M	60 (30-70)	300*	110	90	70
	S	30 (30-70)		110	(90)	70
Nortriptyline	M	150 (25-150)	230	120	90	50
	S	50 (25-150)		140	70	50
Paroxetine	M	20 (30)		110	(90)	70
	S	20 (30)		130	(70)	20
Venlafaxine	M	150 (20-225)		130	(80)	20
CYP2C19-dependent Amitriptyline	M	150 (50-150)		110	80	60
Clomipramine	S	50 (100-200)		100	(90)	70
Citalopram	M	20 (40)		100	(80)	60
Imipramine	M	150 (25-100)		100	(80)	60
	S	50 925-100)		100	(90)	70
Moclobemide	M	600 (300-600)		100	80	70
	S	300 (300-600)		110	80	60
Trimipramine	S	150 (300)		110	(70)	40

Table 1. Summary of Preliminary Average Dose Recommendations for Antidepressant Drugs Differentiated for Single-Dose and Maintenance Treatment

*Recommendations based on sparse data (1 intermediate metabolizer or 1 poor metabolizer)

UM - ultrarapid metabolizer; EM - extensive metabolizer; IM - intermediate metabolizer; PM - poor metabolizer. M/S dosage recommendations for multiple dosing (M - maintenance treatment) or beginning treatment (S - single-dose). Usual Dose - usually applied dose recommended for inpatients, without gene polymorphism considered, as taken from manufacturer's recommendations. (*Parentheses show range of doses given in studies. Recommendations for intermediate metabolizers are estimations based on analogy and require clinical confirmation, Kirchheiner J, et al. Acta Psychiatr Scand. 2003;304:173-192.)

http://www.amplichip.us/physicians/abouttheamplichip.php



Some of the widely prescribed drugs metabolized by CYP2D6

Beta Blockers	Antidepressants	Antipsychotics	Others
Carvedilol	Amitriptyline	Haloperidol	Atomoxetine
Metoprolol	Clomipramine	Risperidone	Codeine
Propafenone	Desipramine	Thioridazine	Dextromethorphan
Timolol	Imipramine		Flecainide
	Paroxetine		Mexiletine
	Venlafaxine		Ondansetron
			Tamoxifen
			Tramadol

Some of the widely prescribed drugs metabolized by CYP2C19

Proton Pump Inhibitors	Anti-epileptics	Others
Omeprazole	Diazepam	Amitriptyline
Lansoprazole	Phenytoin	Clomipramine
Pantoprazole	Phenobarbitone	Cyclophosphamide
		Progesterone

http://www.amplichip.us/physicians/abouttheamplichip.php

HIV: Pharmacogenomics and Public Health

- Variant, Atypical, and Resistant HIV Surveillance (VARHS) is a CDC-funded initiative focused on
  - HIV Drug Resistance (determining what drugs an individual will respond to)
  - HIV Subtype Classification (looking for non-B subgroups)
- Genotypes all newly diagnosed HIV cases
  - Returns results to clinical providers – FREE of charge
  - Over 75% of all individuals in Michigan testing today are offered this service (and growing!)
- Michigan has genotyped over 450 specimens
  - 1 in 7 individuals are infected with a drug-resistant strain of HIV
  - 10% of Michigan cases are non-B subgroups

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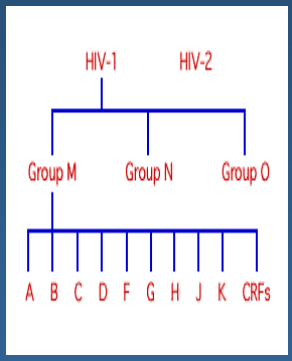
HIV Classification

- 2 known strains of HIV (1 & 2)
  - In the US and Europe HIV-1 is dominant
  - HIV-2 mainly in West African nations
- HIV-1 is divided into 3 groups - M, N & O
  - N & O represent a small percentage found primarily in West-Central Africa and Cameroon respectively
  - M is widespread globally
- Group M is divided into 9 "pure" subtypes: A, B, C, D, F, G, H, J, and K, as well as recombinant (combined) forms
  - In the US, the prevalence of non-B subtypes is still relatively low in most areas



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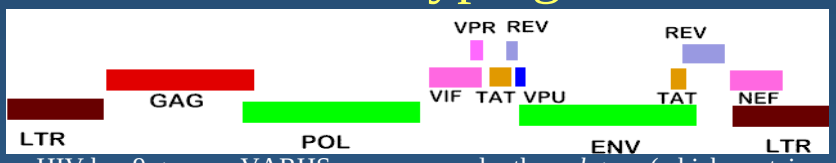
Genotyping



- HIV has 9 genes – VARHS sequences only, the *pol* gene (which contains regions that code for the reverse transcriptase and protease enzymes)
- All mutations (changes from wild or common type) in the *pol* gene's sequence, regardless of their effect on HIV drugs, will be determined
- This mutation information will create a "virtual phenotype" or a prediction of the gene sequence's effect on HIV drugs by comparing it to a large database of many known sequences that have been tested for their response to different drugs in the lab
- Sequences in the *pol* gene will also determine the HIV subtype

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Informed Consent

- Consent is waived because:
  - **VARHS does NOT adversely affect the rights and welfare of individuals**
    - HIV-negative individuals not subjected to consent process
    - All safeguards that protect confidentiality for HIV testing by MDCH apply
  - **VARHS provides information to individuals**
    - ARVDR testing and project information available to individuals returning for HIV test results
    - Individuals can specify clinicians to receive results
  - **VARHS is conducted to evaluate potential changes in an existing program**

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Training/Informing CTR Staff

- VARHS Project Summary Sheets have been distributed to all sites submitting specimens for HIV testing to the MDCH regional labs
- A powerpoint (or similar) presentation can be scheduled for any CTR site upon their request
- MDCH is in receipt of a wide variety of information from non-profit, governmental, and pharmaceutical sources that present topics ranging from drug therapy recommendations to drug resistance and resistance testing that are available upon CTR site request

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Public Health VARHS Benefits

- Determine the distribution of viral genotypes among individuals newly diagnosed with HIV
- Evaluate the effectiveness of risk reduction interventions among treated individuals (how many people on ARVDT are transmitting HIV)
- Chart a course for vaccine studies if prevalence of HIV-1 non-B subtypes is increasing
- Impact treatment guidelines if resistance is found to associate with certain HIV subtypes
  - There is some evidence that certain subtypes are more susceptible to resistance

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Individual Client VARHS Benefits

- Provide reassurance to individuals whose strains are fully susceptible to drugs currently available
- Support reasonable strategies to optimize treatment in individuals whose strains demonstrate resistance
- Capture mutations before they become undetectable (within the 2 year window following infection), providing treatment insight otherwise lost
- Provide a potential benefit to individuals whose clinician for any reason would like to have ARVDR results but can not justify their cost under current guidelines

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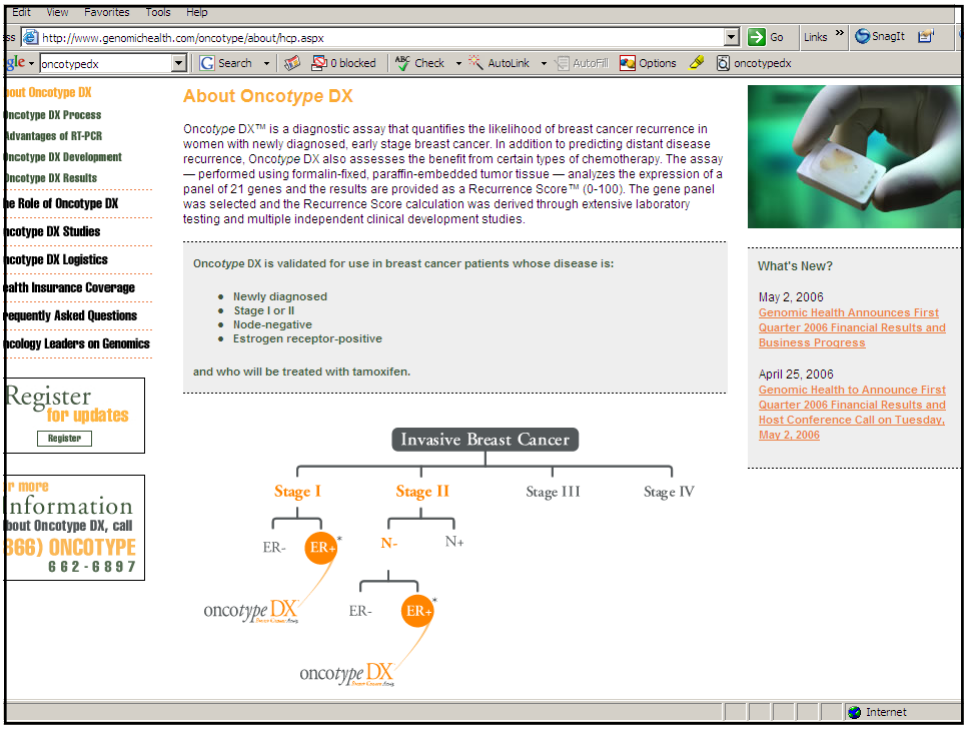
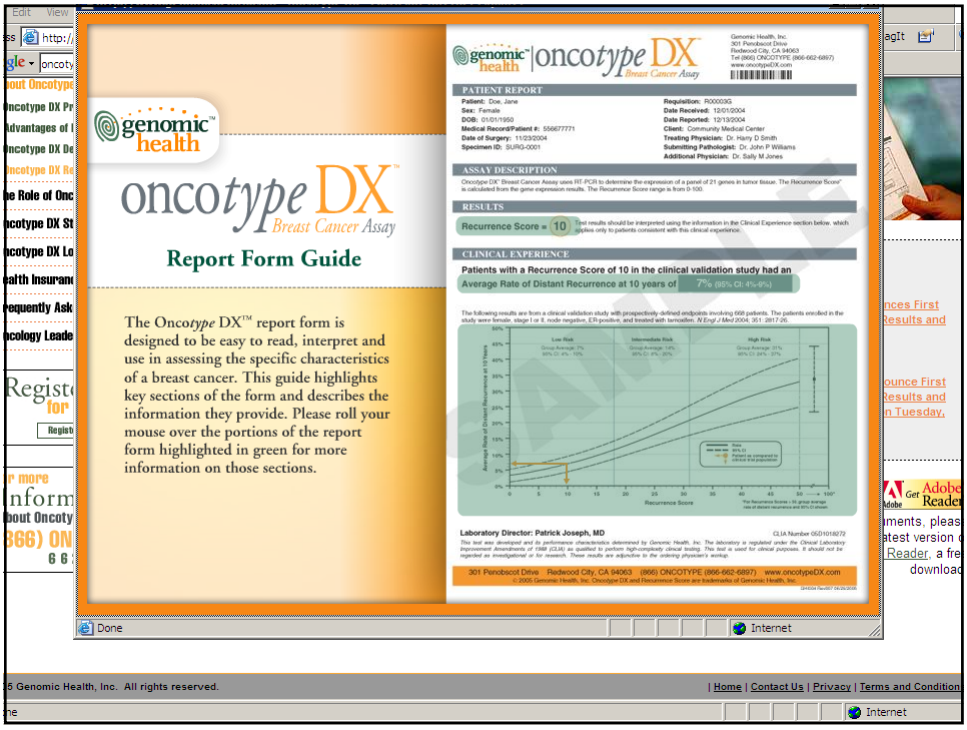

About Oncotype DX
Oncotype DX™ is a diagnostic assay that quantifies the likelihood of breast cancer recurrence in women with newly diagnosed, early stage breast cancer. In addition to predicting distant disease recurrence, Oncotype DX also assesses the benefit from certain types of chemotherapy. The assay — performed using formalin-fixed, paraffin-embedded tumor tissue — analyzes the expression of a panel of 21 genes and the results are provided as a Recurrence Score™ (0-100). The gene panel was selected and the Recurrence Score calculation was derived through extensive laboratory testing and multiple independent clinical development studies.
Oncotype DX is validated for use in breast cancer patients whose disease is:
Newly diagnosed
Stage I or II
Node-negative
Estrogen receptor-positive
and who will be treated with tamoxifen.
What's New?
May 2, 2006
Genomic Health Announces First Quarter 2006 Financial Results and Business Progress
April 25, 2006
Genomic Health to Announce First Quarter 2006 Financial Results and Host Conference Call on Tuesday, May 2, 2006
Invasive Breast Cancer
Stage I
Stage II
Stage III
Stage IV
ER-
ER+
N-
N+
oncotype DX


genomic health
oncotype DX
Breast Cancer Assay
Report Form Guide
The Oncotype DX™ report form is designed to be easy to read, interpret and use in assessing the specific characteristics of a breast cancer. This guide highlights key sections of the form and describes the information they provide. Please roll your mouse over the portions of the report form highlighted in green for more information on those sections.
PATIENT REPORT
ASSAY DESCRIPTION
RESULTS
Recurrence Score = 10
CLINICAL EXPERIENCE
Patients with a Recurrence Score of 10 in the clinical validation study had an
Average Rate of Distant Recurrence at 10 years of
Laboratory Director: Patrick Joseph, MD
Done
Internet
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Barriers to Pharmacogenomics

- Complexity of finding genetic markers (RFPs) that affect drug response
- Limited drug alternatives
- Disincentives for drug companies to make multiple pharmacogenomic products
- Educating healthcare providers

Ethical Issues

- Privacy
- Access to Results
- Patents
- Cost
- Health disparities

Secretary Advisory's Committee on Genetics, Health and Society (SACGHS)

- Explore, analyze, and deliberate on broad range of human health and societal issues raised by development and use, as well as potential misuse, of genetic technologies and make recommendations to Secretary of Health and Human Services, and other entities as appropriate.
  - 2006 topic is pharmacogenomics

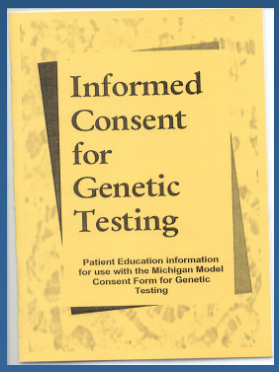
http://www4.od.nih.gov/oba/SACGHS/public_comments.htm

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

- 3 year model project launched by CDC in 2005
- Aims: Establish systematic evidence-based process for assessing genetic tests and genetic technology in transition from research to clinical and public health practice
  - CYP450 for SSRIs is one of four tests being evaluated

http://www.ahrq.gov/clinic/tp/cyp450tp.htm

Genetic Counseling and Testing in Michigan



http://www.migeneticsconnection.org/geneticliteracy.shtml

National and State Resources

- National Human Genome Research Institute
  - http://genome.gov
- US Department of Energy Human Genome Project
  - http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml
- Centers for Disease Control: Genomics and Disease Prevention
  - http://www.cdc.gov/genomics/default.htm
- Michigan Department of Community Health: Michigan Genetics Resource Center
  - http://www.migeneticsconnection.org
- Michigan Center for Genomics and Public Health
  - http://www.sph.umich.edu/genomics

Public Health Genomics Team

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- Mark Caulder, MS, MPH
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- Mary Teachout, MAT
  - Genomics Educator
- Valerie Ewald
  - Administrative Assistant

Acknowledgements

•Mary-Grace Brandt, PhD, MPH- MDCH HIV Drug Resistance Surveillance Coordinator

•Keith Johnson, PhD- Pharmacogenomics, Pfizer

•Thomas Monroe, PhD and Kim Collison, MSA, MT- Spectrum Health Laboratory

- For more info on Spectrum Health's CYP450 testing, contact (616) 391-7568, kim.collison@spectrum-health.org or thomas.monroe@spectrum-health.org

This presentation is supported in part by Cooperative Agreement #U58/CCU522826 from CDC. Its contents are solely the responsibility of the presenter and do not necessarily represent the official views of CDC.